REMARKS:

Claims 1-3, 5, 6 and 8-19 are in the case and presented for consideration.

Claim 1 has been amended to improve its form.

Claims 4, 7 and 20-25 were previously canceled, all subject to Applicants' right to claim their subject matter in one or more continuing applications.

At the outset, Applicants respectfully highlight that Claim 1 has already been amended to clarify that the claimed technical solution is directed to pharmaceutical composition containing (OC-6-43)-bis(acetato)-(1-adamantylamine)-amine-dichloroplatinic platinum complex of formula (II) as an active substance in a mixture with at least one pharmaceutically acceptable excipient wherein it is formed of a granulate with particles smaller than 0.5 mm in size prepared by wet granulation of a mixture of platinum complex of tetravalent platinum of formula (II) wetted by water, at least one neutral saccharide and at least one native and/or modified polysaccharide. See Amendment and Response dated April 27, 2009. Support for that amendment may be found at least at paragraphs [0020], [0021], [0028], [0039], [0040] and [0041] of the published application.

Rejection Under 35 U.S.C. §112

Claims 1-3, 5-6 and 8-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The official action states that the claims contain new subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the Office states that nowhere in the specification is there basis for "contained in a sack and pressed into a tablet" The Office states that the specification, at page 3, line 20-21 recites "[t]he pharmaceutical composition according to the invention is advantageously contained in a capsule or a sack or is pressed into a tablet form" not in a sack and pressed into a tablet form as recited.

Applicant respectfully submits that these two elements of a Markush group may have been understood by the Office to be a single element. Claim 1 has been amended to insert an additional comma, so as to clarify that “contain in a sack” and “pressed into tablet form” are two separate items in the Markush group.

Claim 1 is therefore believed to be in condition for allowance.

Rejections Under 35 U.S.C. §103(a)

Claims 1-11 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,503,943 Zak et al. (“Zak et al.”), in view of U.S. Patent No. 6,221,393 to Collaueri et al. (“Collaueri et al.”), and further in view of U.S. Patent No. 5,275,824 to Caril et al. (“Caril et al.”). Official Action at p. 5.

For the reasons that follow, Applicants respectfully traverse this rejection.

Graham v. John Deere, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) outlined the approach that must be taken when determining whether an invention is obvious 35 U.S.C. §103(a).

In *Graham*, the Court stated that a patent may not be obtained if the subject matter would have been obvious at the time the invention was made to a person having ordinary skill in the art, and emphasized that non-obviousness must be determined in the light of inquiry, not quality (supra at page 467). In accordance with *Graham*, these inquiries must be made in determining whether an invention is obvious:

(1) The scope and content of the prior art are to be determined.

(2) The differences between the prior art and the claims at issue are to be ascertained.

(3) The level of ordinary skill in the pertinent art resolved.

(4) Objective evidence relevant to the issue of obviousness.

The Applicant will now set forth his analysis of obviousness in view of the requirements of *Graham v. John Deere* and the Office Action issued by the Examiner.

Ascertaining the level of ordinary skill in the art at the time Applicant discovered its process is impractical in an *ex parte* proceeding since neither the Examiner nor the Applicant have survey evidence related to the qualifications of the technical people working in this field, or the testimony of an expert witness familiar with the qualifications of the technical people working in this field. In view of this, Applicant submits that the only facts of record pertaining to the level of skill in the art are found within the prior art of record.

Applicant further submits, based upon its review of the prior art of record and the prior art in this field related to platinum complexes, the art is crowded and

advancements in the art are incremental. In Applicant's view, deriving inventions in this field is like looking for the proverbial "needle in the haystack."

When considering whether Applicant's claimed invention is obvious, Applicant asks the Examiner to recognize the danger of employing "hindsight" in his/her analysis, particularly in a field where the art is crowded and improvements in the technology are incremental. This danger is inherent in the examination process since the Examiner knows what the invention is when he/she determines whether Applicant's invention is obvious. On the other hand, the only information Applicant has at the time of its discovery are the teachings of the prior art, so the inquiry related to obviousness must focus on the content of what the prior art teaches and suggests to the person of ordinary skill in the art at the time the invention was made. In this regard, Applicant hopes that the Examiner will keep in mind the following comments excepted from *In re Kotzab*, 55 U.S.P.Q. 2d 1313 (Fed. Cir. 2000) at page 1317:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher." *Id.* (quoting *W.L. Gore & Assocs., Inc., v Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303,313 (Fed. Cir. 1983).

In reference to how (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex could be formulated, Zak et al. state, "it may be administered...*in suitable application form*" (see col. 6, lines 16-17). Applicants respectfully submit that a person of ordinary skill in the art aspiring to prepare any specifically formulated composition of the above-mentioned platinum (IV) complex

could not have found in Zak et al. any usable teaching since the statement "in suitable application form" provides no teaching at all. Consequently, it is submitted that the subject matter of the presently-claimed invention would have by no means been obvious in view of Zak et al. for a person of ordinary skill in the art. Thus, subject-matter of the presently-claimed invention should be deemed non-obvious over Zak.

To be sure, Zak et al. is not *at all* relevant for assessing the non-obviousness of the presently-claimed invention. Such a reference should at least provide a solution to the technical problem to be solved, but Zak et al. does not in any way provide such a solution. Therefore, the Applicants respectfully submit that Zak et al. has no bearing on the non-obviousness of the presently-claimed invention.

Regarding Collaueri et al., Applicant respectfully submits that Collaueri' et al.'s wet granulation is *not* wet granulation during which excipients and an active ingredient *are wet granulated together*. The Office's interpretation in this regard is respectfully traversed since excipients and the active ingredients are actually wet granulated separately. In this vein, the Applicants refer to their previous response in which they pointed to direct evidence of separately-implemented wet granulation. For example, Applicants noted,

> Collaueri et al. teaches, analogously to Kaplan et al., a separate wet granulation of an excipient (xanthan gum), only, rather than the wet granulation of an active ingredient together with the excipients; the obtained pregranulated xantham gum is afterwards dryblended with the active ingredient and optionally with the other used excipients. It is evident that Collaueri et al. does not solve, either, the problem of the substances showing the above-mentioned undesirable properties. This is because those substances

> remain at their original form, still exhibiting the above-mentioned undesired properties and influenced by no means by the wet granulation of the excipients with which the substances are later dryblended and optionally further worked.

Amendment and Response Dated 5/21/10 at p. 16.

Again, Applicants explained:

> The person skilled in the art would have been instructed by Kaplan et al. and Collaueri et al. that if the wet granulation is used, at all, then only the excipient(s) are separately (i.e. without active ingredient) wet granulated. This would have taught the person skilled in the art away from implementing the common wet granulation of the active ingredient together with the excipients. This practically, in turn, means that the condition of the point (b) necessary for denying the non-obviousness of the subject matter of the presently-claimed invention is not provided by Kaplan et al. and Collaueri et al.

Id. at p. 19.

In response, the present official action states only that "Table 1 teaches the procedure is by wetting, therefore one of ordinary skill in the art would necessarily expect that the process is by wet granulation." Official Action at p. 5. It is respectfully submitted that this interpretation stands at variance with the teaching of Collaueri et al. Applicants respectfully disagree with the understanding of the term "wetting" as reflected in this statement from the official action. Table 1 mentions a "wetting angle" by means of which the wettability of tablets is determined. This wettability has nothing to do with the wet granulation. In fact, there is a great difference between a non-separately and separately-implemented wet granulation. When the active ingredient is not granulated together with the excipients but only admixed to the previously wet-

granulated excipients (as it is done according to Collaueri et al.), the active ingredient is not exposed to the relatively severe conditions of the wet granulation and is thus protected against an optional disintegration, which could be the case for the very sensitive platinum (IV) complexes. Therefore, if the Applicant, notwitstanding, decided, contrary to the teaching of Collaueri et al., to protect the active ingredient by way of non-separately implementing wet granulation he had surely no reasonable expectation of success, which evidences strongly in favor of the non-obviousness of the presently-claimed invention over Collaueri et al.

With respect to Caril et al., the Office asserts that this reference "teaches therapeutic compositions with controlled release medicaments that are coated with polymeric films formed by wet granulation," Official action at p. 7, which should produce the impression that the wet granulation is the only working step that should be implemented to obtain the mentioned therapeutic compositions and that such wet granulation is hence comparable, in terms of the chosen working method, to the wet granulation according to the present application. Applicants respectfully submit that this is not in accordance with that is taught in the reference.

Caril et al.'s therapeutic composition is prepared using a process including the steps of:

> 1) loading the particles of water-insoluble but water-swellable polymer with the required medicament either [1(a)] by swelling with solutions of the medicament followed by drying, or [1(a)] by high-energy co-grinding;
>
> 2) suspending such loaded polymer particles, of between 1 and 200 .mu.m, in a current of air in a fluidized bed apparatus, spraying them with a solution of the coating

> polymer, and then drying them in the same apparatus or by another method;
>
> 3) size-enlarging the medicament-loaded polymer particles by wet or dry granulation...

col. 2, ll. 40-54.

Step (3) of Caril et al.'s preparative process has evidently only a facultative and auxiliary character, which means that it is used only under the condition that it is required to convert the powder particles issued from the step (1) into granules before covering them with a coating polymer. Nevertheless if step (3) is employed, it is clear that a mixture of the used excipients and medicament (active ingredient), having to be subjected to the wet granulation, is previously specifically processed in step (1) (either (1a) by swelling with solutions of the medicament followed by drying, or (1b) by high-energy co-grinding). But no such previous treatment of the mixture of excipients and active ingredient is implemented when the wet granulation according to the present application is realized. On the contrary, the excipients and the active ingredients are simply mixed and directly wet-granulated in the latter case.

This is a significant difference since -- whereas the interaction of excipients/medicament having, in turn, principal impact on release characteristics of the medicament is already established during the mentioned step (1) and substantially not during the following wet granulation (which, incidentally, need not be used at all) -- the same interaction is established for the composition according to the presently-claimed invention until during the wet granulation alone. This difference is naturally translated into differences in structure between Caril et al.'s granulate and that of the presently-

claimed invention. In addition, Caril et al.'s preparative process expressly uses, as starting material, crosslinked polymers or material comprising a lattice (see col. 4, lines 40-62) which is not the case at all with the wet granulation according to the presently-claimed invention. In fact, the polysaccharides used in the wet granulation according to the present application are branched but do not comprise a lattice, neither are they crosslinked. It follows from the foregoing, that the person skilled in the art working to prepare a stable pharmaceutical composition of a specific platinum (IV) complex would not have found in Caril et al., any motivation to (1) pass from the intricate Caril et al. preparative process, in which the wet granulation is used as a mere auxiliary non-indispensable step only, to the preparative process according the presently-claimed invention consisting of the only wet granulation step using, in addition, starting excipients different from those used by Caril et al.; and (2) use at least one neutral saccharide and at least one native and/or modified polysaccharide in the presence of which the specific platinum (IV) complex unexpectedly appeared to be stable during the wet granulation.

Even when the person skilled in the art would have hypothetically started from Caril et al.'s process, it is evident that the large modifications of Caril et al.'s process -- represented by the difference between the Caril et al.'s process and the process used in framework of the presently-claimed invention and quite changing the character of Caril et al.'s process -- would not surely have created in such a person with a reasonable expectation of success. This fact strongly evidences in favor of the non-obviousness of the subject-matter of the present application over Caril et al.

The technical problem to be solved by the presently-claimed invention application was to face the unsuitable physical properties of (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex (e.g., insolubility in water, small bulk density, small tap density and high electrostatic charge) on the one hand, and the chemical instability of this platinum complex in contact with commonly used pharmaceutical excipients, on the other hand, when preparing a highly stable pharmaceutical composition of the mentioned platinum complex. The Applicant has solved this problem by wet granulating (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex *together with* a neutral saccharide and a native and/or modified polysaccharide.

As shown above, Zak et al. offers no solution to the outlined technical problem. A person of ordinary skill in the art could by no means have derived the presently-claimed, unexpected solution from Collaueri et al. either, since Collaueri et al. wet-granulate the excipients only, i.e. without the active ingredient. The non-wet granulated active ingredient is only afterwards mixed with the wet-granulated excipients. Collaueri et al. does not in fact solve the problem of the unsuitable physical properties of (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex since this platinum complex keeps through the full Collaueri et al. process its discrete cumbersome powder form, which is not firmly incorporated into matrix of granulate. In addition, the fact alone that Collaueri et al. avoids the common wet granulation of excipients with the active ingredient, in turn, means that the Collaueri et al. actually teaches *away* from the common wet granulation as claimed by applicant's in the presently-claimed invention.

Even if the Caril et al.'s wet granulation is regarded -- for purposes of comparison with the wet granulation according to the presently-claimed invention -- as a proper working step forming the basic structure of excipients/active ingredient (which, actually, is not the basic structure since said basic structure is already formed during the Caril's step (1) and the wet granulation step (3) serves only as a means for *optionally* enlarging the particle size of the previously formed basic structure), it should be emphasized that the Caril et al.'s wet granulation needs to be preceded only by step (1) in which the active ingredient is previously linked either to surface of the swelled excipients (if step (1) is realized by swelling with solutions of the medicament) or to freshly exposed faces of the excipients (if the step (1) is realized by high-energy co-grinding).

As it is, the mere fact that the step (1) is necessary for the Caril et al.'s wet granulation clearly evidences in favor of the view that Caril et al. in fact could have by no means been useful as basis for deriving the wet granulation avoiding step (1), i.e. the wet granulation according to the presently-claimed invention, all the more so that the active ingredient is obliged to confront, during Caril et al.'s process, not only the working conditions of the wet granulation but also the severe working conditions of step (1) which would not have been acceptable to persons of ordinary skill in the art dealing with the very unstable (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex.

In addition, it is evident that the cited prior art documents, considered together, would not have been able to lead the person skilled in the art to the Applicant´s

solution, either. Both Collaueri et al. and Caril et al. in fact *discourage* the person skilled in the art from departing from their teachings, respectively.

Additionally, the conditions under which the Collaueri et al.'s and Caril et al.'s wet granulations are carried out are very different from those used during the wet granulation of the presently-claimed invention as a result of which the structure of the composition according to the present application is different from those of Collaueri et al. and Caril et al., so that the composition according to the presently-claimed invention represents product being structurally novel over the relevant prior art. Consequently, the effect reached by the solution according to the present application, i.e. stability of (OC-6-43)-bis(acetato)-(1-adamantylamine)-ammine-dichloroplatinic platinum complex in the obtained composition was not obviously derivable from the prior art.

In view of the foregoing, Applicants respectfully submit that the presently-claimed invention was not obvious over the cited references - either individually or in combination - and that the present application should be deemed in condition for allowance.

Conclusion

Accordingly, Applicants believe that all the claims are now in condition for allowance and favorable action is respectfully requested. Should there be any issues that have not been addressed to the Examiner's satisfaction, Applicants invite the Examiner to contact the undersigned attorney.

If any fees other than those submitted herewith are due in connection with this response, please charge such fees to Deposit Account No. 14-1431.

Respectfully submitted,

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